NCT03001011

AMENDED CLINICAL TRIAL PROTOCOL NO. 02

COMPOUND: Renvela® /sevelamer carbonate/GZ419831

A randomized, double blind, parallel group study for assessing the efficacy and safety of Renvela® tablets for the treatment of hyperphosphatemia in patients with chronic kidney disease not on dialysis versus placebo (RECOVER Study)

STUDY NUMBER: EFC14011

STUDY NAME: RECOVER Study

VERSION DATE / STATUS: Approval date (13-Apr-2018) / Approved

Protocol Amendment 02	Version number: 1 (electronic 1.0)	Date : 13-Apr-2018
Amended Clinical Trial Protocol 01	Version number: 1 (electronic 1.0)	Date : 13-Dec-2017
Protocol Amendment 01	Version number: 1 (electronic 1.0)	Date : 13-Dec-2017
Clinical Trial Protocol	Version number: 1 (electronic 1.0)	Date : 07-Nov-2014

Version Number:	1	EudraCT IND Number(s) WHO universal trial number	Not applicable Not applicable U1111-1161-9850
Date:	13-Apr-2018	Total number of pages:	69

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: Renvela®/sevelamer carbonate/GZ419831	**STUDY No: EFC14011 STUDY NAME : RECOVER Study**
TITLE	A randomized, double blind, parallel group study for assessing the efficacy and safety of Renvela® tablets for the treatment of hyperphosphatemia in patients with chronic kidney disease not on dialysis versus placebo
INVESTIGATOR/TRIAL LOCATION	China only
PHASE OF DEVELOPMENT	III
STUDY OBJECTIVE(S)	**Primary Objective** • The primary objective of this study is to demonstrate efficacy of Renvela® tablets in the reduction of serum phosphorus in hyperphosphatemia in patients with chronic kidney disease (CKD) not on dialysis. **Secondary Objective(s)** • To document the efficacy of Renvela tablets in the reduction of serum lipids (total cholesterol and low-density lipoprotein cholesterol [LDL-C]). • To document the efficacy of Renvela tablets in the reduction of calcium-phosphorus product. • To document the efficacy of Renvela tablets in the reduction of intact parathyroid hormone (iPTH). • To document the efficacy of Renvela tablets in proportion of patients reaching the target serum phosphorus level (4.6 mg/dL [1.49 mmol/L], inclusive). • To evaluate safety of Renvela tablets.
STUDY DESIGN	This is a randomized, double blind, parallel group, dose titration study to evaluate efficacy and safety of Renvela tablets versus placebo. This study is divided into 3 periods: Screening Period (for patients who are not on phosphate binder[s] at Screening Visit 1, the Screening Period is up to 10 days; for patients who are on phosphate binder[s] at Screening Visit 1, a 2-week Washout period is needed before Post-Washout Screening Visit 1a [The time window of V1 and V1a is up to 10 days, respectively. However, the total time window of V1 and V1a should not exceed 14 days to ensure the total duration of screening period is up to 4 weeks), Treatment Period (8 weeks) and Post-treatment Period (2 weeks). Hyperphosphatemia patients with CKD not on dialysis will be screened for eligibility. Eligible patients will be randomized 1:1 to Renvela tablets or placebo arm. Stratification factor is screening serum phosphorus (≥5.5 - 6.0 mg/dL [1.78 – 1.94 mmol/L] and >6.0 mg/dL [1.94 mmol/L]). For eligible patients who are not taking phosphate binder(s) at screening visit, serum phosphorus at V1 will be used for stratification. For eligible patients who are taking phosphate binder(s) at screening visit, serum phosphorus at V1a will be used for stratification.
STUDY POPULATION **Main selection criteria**	Chronic kidney disease has been defined according to the criteria: 1. Kidney damage ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased Glomerular

	Filtration Rate (GFR), manifest by either: • Pathological abnormalities; or • Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests. 2. GFR <60 mL/min/1.73 m^2 for ≥3 months, with or without kidney damage. **Inclusion Criteria**: I 01. Patients with chronic kidney disease who have not been on dialysis, and are not expected to begin dialysis, or renal transplantation in the next 4 months from the Screening Visit. I 02. Have serum phosphorus measurement ≥5.5 mg/dL (1.78 mmol/L) at Screening Visit (if patients are not on phosphate binder[s] at Screening Visit) **OR** at the end of Washout Period (if patients are on phosphate binder[s] at Screening Visit). I 03. Have the following laboratory measurements at Screening Visit: • 25-hydroxy vitamin D ≥5 ng/mL • iPTH ≤800 pg/mL. I 04. Signed written informed consent. **Exclusion Criteria :** E 01. Men or women below 18 years of age. E 02. Is not of the level of understanding and willingness to cooperate with all visits and procedures, as described in the study protocol. E 03. Not yet received CKD diet education before Screening Visit. E 04. Not willing and not able to avoid changes to diet during the study. E 05. Not willing or not able to maintain screening doses of lipid lowering medication, 1, 25 dihydroxy vitamin D, and/or cinacalcet for the duration of the study, except for safety reasons. E 06. Not willing or not able to avoid antacids and phosphate binders containing aluminium, magnesium, calcium or lanthanum for the duration of the study unless prescribed as an evening calcium supplement. E 07. Have participated in any other investigational drug studies within 30 days or 5 half-lives, whichever is longer, prior to Screening Visit. E 08. Have known hypersensitivity to sevelamer or any constituents of Renvela tablets. E 09. Have bowel obstruction, active dysphagia, swallowing disorder, a predisposition to or current bowel obstruction, ileus, or severe gastrointestinal motility disorders including severe constipation. E 10. Using or plan to use anti-arrhythmic or anti-seizure medications for arrhythmia or seizure disorders. E 11. Is pregnant or breast-feeding. E 12. If the patient is female, and of childbearing potential (such as pre-menopausal and not surgically sterile, postmenopausal women who are amenorrheic for less than12 months), is not willing to use an effective contraceptive method throughout the study. E 13. Have any condition, which in the opinion of the investigator would prohibit the patient's inclusion in the study.

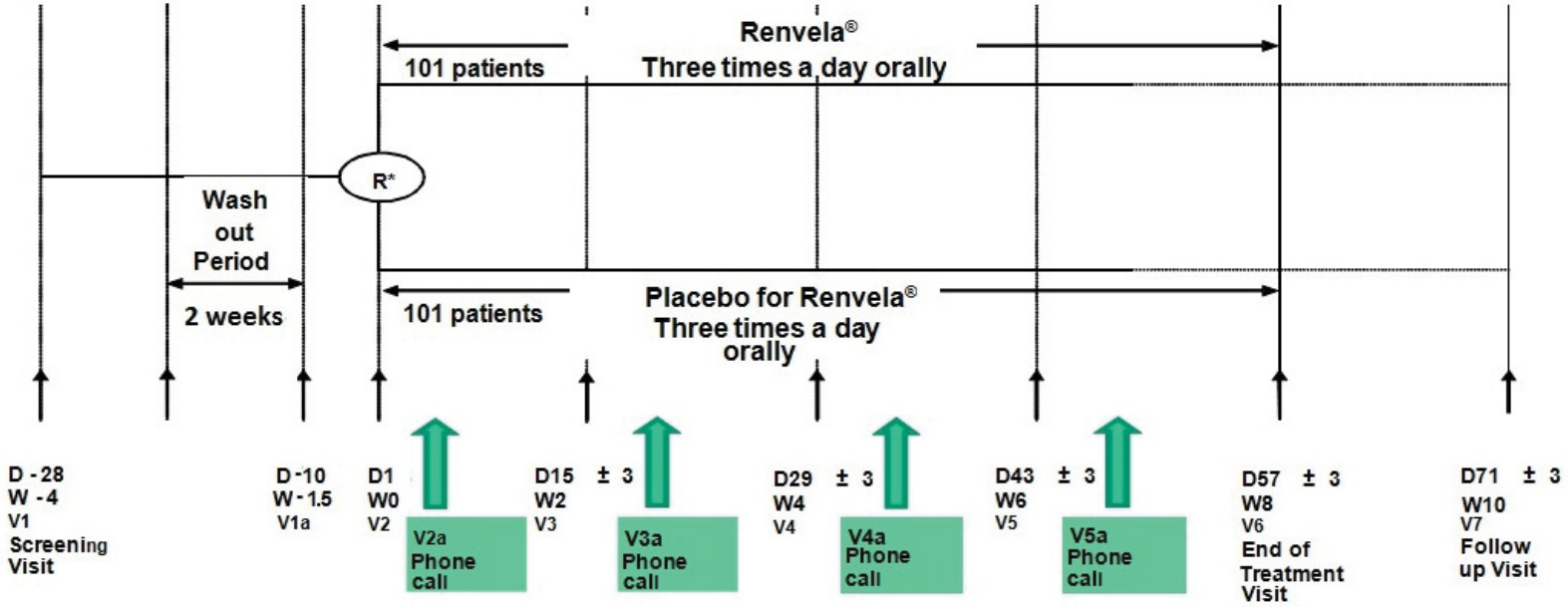
Total expected number of patients **Expected number of sites:**	Approximately 202 patients will be randomized. Approximately 20-40 sites will join this study.
STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation**	Renvela® (sevelamer carbonate) or matching placebo 800 mg/tablet
Route(s) of administration	Taken orally with meal
Dose regimen	The starting dose of the study treatment is 1 tablet (if serum phosphorus is between 5.5 – 7.5 mg/dL [inclusive] at screening) or 2 tablets (if serum phosphorus is >7.5 mg/dL at screening) of Renvela or placebo 3 times per day (TID) with meals. For eligible patients who are not taking phosphate binder(s) at screening visit, serum phosphorus at V1 will be used for determination of the starting dose. For eligible patients who are taking phosphate binder(s) at screening visit, serum phosphorus at V1a will be used. In order to adjust the deviation of starting dose based on phosphorus at screening, after the phosphorus result at V2 is received from the central laboratory, a dose adjustment phone call at V2a (as soon as possible once serum phosphorus at V2 is available) will be made by the investigator to instruct patients to adjust their IMP starting dose, if dose adjustment is needed. The adjusted dose at V2a is 1 tablet (if serum phosphorus is $\leq$7.5 mg/dL at V2) or 2 tablets (if serum phosphorus is >7.5 mg/dL at V2) of Renvela or placebo 3 times per day (TID) with meals. During the Treatment Period, patients return to the investigative site every 2 weeks. Samples for laboratory measurements are collected at each site visit. After the results are received from the central laboratory, the serum phosphorus results are evaluated. If the serum phosphorus is ≥4.6 mg/dL (≥1.49 mmol/L), the patient is to be instructed by the investigator to increase their study treatment dose by 1 tablet TID with meals. If the serum phosphorus is <2.7 mg/dL (<0.87 mmol/L), the patient is to be instructed by the investigator to decrease their study treatment dose by 1 tablet TID with meals. Therefore, the potential maximal dose could be up to 15 tablets a day. At the End of Treatment Period, study treatment is stopped and patients will be followed up for 2 weeks.
Noninvestigational medicinal product(s) (if applicable)	Native Vitamin D
Formulation	Drops
Route(s) of administration	Taken orally
Dose regimen	400 IU/day
ENDPOINT(S)	**Primary Endpoint:** The change from baseline in serum phosphorus level at Week 8 **Secondary Endpoint(s):** • The change from baseline in total cholesterol at Week 8 • The change from baseline in LDL-C at Week 8 • The change from baseline in calcium-phosphorus product at Week 8 • The change from baseline in iPTH level at Week 8 • Percentage of patients reaching the target serum phosphorus level

	(4.6 mg/dL [1.49 mmol/L], inclusive) at Week 8 • The change from baseline in serum phosphorus level at Week 4 **Safety Endpoint(s):** • Proportion of patients with adverse events • Clinically significant changes in vital signs and clinical laboratory parameters
ASSESSMENT SCHEDULE	V1 (Week -1.5 [Day -10 to Day -1] for patients **not on** phosphate binder[s]; Week -4 [Day-28 to Day -19] for patients **on** phosphate binder[s]): Screening Visit. V1a (Week -1.5 [Day -10 to Day -1] for patients **on** phosphate binder[s]): Post-Washout Visit for patients on phosphate binder(s) at Screening Visit. V2 (Day 1): Randomization; first Renvela or placebo tablets administration; baseline. V2a (phone call visit): Patients will be contacted by phone if adjustment of the starting dose of IMP based on serum phosphorus level at V2 is needed. V3 (Week 2), V4 (Week 4) and V5 (Week 6): Efficacy and safety assessments. V3a, V4a and V5a (phone call visits): Patients will be contacted by phone if dose titration based on serum phosphorus level of V3, V4 and V5 is needed. V6 (Week 8): End of treatment, last Renvela or placebo tablets administration. V7 (Week 10): Follow up visit. For all visits (except phone call visits), a time frame of ±3 days is acceptable using Day 1 as reference.
STATISTICAL CONSIDERATIONS	**Sample size determination:** To detect a difference of 1 mg/dL in the change from baseline in serum phosphorus between Renvela and placebo at Week 8, 86 patients per arm will provide the power of 90% assuming the common standard deviation is 2 mg/dL (based on data observed in prior study SVCARB03808) with a 2-sided test at the 5% significance level. With expected dropout rate of 15%, the final total sample size will be 202 patients (101 patients in each arm). **Analysis Population:** • Modified Intention To Treat (mITT) population: The mITT population consists of all patients who are randomized, receive at least one dose of investigational medicinal product (IMP), and have both a baseline assessment and at least one post-baseline assessment of phosphorus measure. • Safety population: The safety population consists of all randomized patients who receive at least one dose of IMP. **Primary Analysis:** The primary efficacy variable (the change from baseline in serum phosphorus at Week 8) will be compared between Renvela and placebo using stratified Wilcoxon rank sum tests considering randomization strata (screening serum phosphorus [≥5.5 – 6.0 mg/dL or >6.0 mg/dL]). **Analysis of secondary endpoints** Change in total cholesterol, LDL-C, calcium-phosphorus product, iPTH and percentage of patients reaching the target serum phosphorus level (4.6 mg/dL

	[1.49 mmol/L], inclusive) at Week 8, and change in serum phosphorus at Week 4 will be analyzed using stratified Wilcoxon rank sum tests using randomization strata (screening serum phosphorus [≥5.5 – 6.0 mg/dL or >6.0 mg/dL]). Percentage of patients reaching the target serum phosphorus level will be compared by treatment assignment (Renvela or placebo) using a Cochran-Mantel-Haensel method stratified by randomization strata (screening serum phosphorus [≥5.5 – 6.0 mg/dL or >6.0 mg/dL]), the odds ratio and 95% confidence intervals will be calculated.
DURATION OF STUDY PERIOD (per patient)	Study duration is up to 14 weeks. • Screening Period is up to 4 weeks (a 2-week Washout Period is only applicable to eligible patients taking phosphate binder[s] at Screening Visit); • Treatment Period is 8 week; • Post-treatment Period is 2 weeks.
STUDY COMMITTEES	**Steering Committee:** ☒ Yes ☐ No **Data Monitoring Committee:** ☐ Yes ☒ No **Adjudication Committee:** ☐ Yes ☒ No

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



- R=Randomization
- Screening criteria:
  - CKD patients not on dialysis
  - Serum phosphorus level ≥5.5 mg/dL (1.78 mmol/L)
- Stratification factor, at the time of randomization, is screening serum phosphorus (≥5.5 – 6.0 mg/dL [1.78 – 1.94 mmol/L] and >6.0 mg/dL [1.94 mmol/L]). For eligible patients who are not taking phosphate binder(s) at screening visit, serum phosphorus at V1 will be used for stratification. For eligible patients who are taking phosphate binder(s) at screening visit, serum phosphorus at V1a will be used for stratification.
- Assessment of the primary efficacy (change from baseline in serum phosphorus level) endpoint is at Week 8.
- Wash out period is only for patients on phosphate binder(s) at screening. Patients not on phosphate binder(s) would proceed directly to the start of the 8-week treatment period (Day 1).
- During the Treatment Period, patients return to the investigative site every 2 weeks. Samples for laboratory measurements are collected at each site visit. After the results are received from the central laboratory, the serum phosphorus results are evaluated. Investigator will be informed by the IVRS/IWRS for dose titration. If the serum phosphorus is ≥4.6 mg/dL (≥1.49 mmol/L), the patient is to be instructed by the investigator to increase their study treatment dose by 1 tablet TID with meals. If the serum phosphorus is <2.7 mg/dL (<0.87 mmol/L), the patient is to be instructed by the investigator to decrease their study treatment dose by 1 tablet TID with meals.

1.2 STUDY FLOW CHART

	Screening Period		Double blind treatment Period									Post-treatment Period
VISIT	1 (Screening Visit)	1a (Post-Washout Visit, only for patients on phosphate binder[s])	2	2a (phone call)	3	3a (phone call)	4	4a (phone call)	5	5a (phone call)	6 (End of treatment visit)	7 (Follow-Up Visit)
DAY	-28 to -19[a] (for patients on phosphate binder[s]) OR -10 to -1 (for patients not on phosphate binder[s])	-10 to -1[a] (only for patients on phosphate binder[s])	1		15±3		29±3		43±3		57±3	71±3
WEEK	-4 (for patients on phosphate binder[s]) OR -1.5 (for patients not on phosphate binder[s])	-1.5 (only for patients on phosphate binder[s])	0		2		4		6		8	10
Describe study and obtain signed written Informed Consent	x											
Review inclusion & Exclusion criteria	x	x	x									
Assign subject number	x											
Demographic history, review medical and renal history & prior medication	x											
Physical exam	x		x		x		x		x		x	
Vital signs	x		x		x		x		x		x	
Body weight	x		x		x		x		x		x	
Height	x											
Serum chemistry panel	x[b]		x[c]		x[d]		x[d]		x[d]		x[c]	

	Screening Period		Double blind treatment Period									Post-treatment Period
VISIT	**1 (Screening Visit)**	**1a (Post-Washout Visit, only for patients on phosphate binder[s])**	**2**	**2a (phone call)**	**3**	**3a (phone call)**	**4**	**4a (phone call)**	**5**	**5a (phone call)**	**6 (End of treatment visit)**	**7 (Follow-Up Visit)**
DAY	**-28 to -19[a] (for patients on phosphate binder[s]) OR -10 to -1 (for patients not on phosphate binder[s])**	**-10 to -1[a] (only for patients on phosphate binder[s])**	**1**		**15±3**		**29±3**		**43±3**		**57±3**	**71±3**
WEEK	**-4 (for patients on phosphate binder[s]) OR -1.5 (for patients not on phosphate binder[s])**	**-1.5 (only for patients on phosphate binder[s])**	**0**		**2**		**4**		**6**		**8**	**10**
Serum phosphorus	x	x	x		x		x		x		x	
Serum 25-OH vitamin D	x											
Calculate and record eGFR	x											
Serum pregnancy test (women of childbearing potential only)	x											
Serum iPTH	x		x		x		x		x		x	
Lipid panel			x[e]								x[e]	
Complete Blood Count, differential, platelet and Prothrombin Time	x		x								x	
IVRS/IWRS contact	x		x		x		x		x		x	x
Randomization			x									
Dispense investigational product			x		x		x		x			

	Screening Period		Double blind treatment Period									Post-treatment Period
VISIT	1 (Screening Visit)	1a (Post-Washout Visit, only for patients on phosphate binder[s])	2	2a (phone call)	3	3a (phone call)	4	4a (phone call)	5	5a (phone call)	6 (End of treatment visit)	7 (Follow-Up Visit)
DAY	-28 to -19[a] (for patients on phosphate binder[s]) OR -10 to -1 (for patients not on phosphate binder[s])	-10 to -1[a] (only for patients on phosphate binder[s])	1		15±3		29±3		43±3		57±3	71±3
WEEK	-4 (for patients on phosphate binder[s]) OR -1.5 (for patients not on phosphate binder[s])	-1.5 (only for patients on phosphate binder[s])	0		2		4		6		8	10
Collect investigational product, perform accountability & compliance check by review of diary					x		x		x		x	
Dispensation and training of patient diary			x									
AE assessment	x	x	x		x		x		x		x	x
Concomitant Medications/Therapies	x	x	x		x		x		x		x	x
Evaluate for dose adjustment and dose titration				x[f]		x[g]		x[g]		x[g]		

a For patients on phosphate binder(s), the time window of V1 and V1a is up to 10 days, respectively. However, the total time window of V1 and V1a should not exceed 14 days to ensure the screening period is up to 4 weeks, including a wash out period which should be 2 weeks (14 days).

b Chemistry panel at Visit 1: Calcium (adjusted for albumin), albumin, calcium-phosphorus product, chloride, bicarbonate and creatinine.

c Chemistry panel at Visits 2 and 6/End of Treatment: Calcium (adjusted for albumin), albumin, calcium-phosphorus product, chloride, bicarbonate, uric acid, sodium, potassium, glucose, blood urea nitrogen, liver function tests (ALT and AST) and creatinine. According to the discretion of the Investigator for safety concern, the relevant laboratory parameters (eg, serum potassium) can be tested at any scheduled visit or unscheduled visit if necessary.

d Chemistry panel at Visits 3, 4, and 5: Calcium (adjusted for albumin), albumin, calcium-phosphorus product, chloride, and bicarbonate.

e Lipid panel includes total cholesterol, LDL-C, HDL-C, non-HDL-C and triglycerides.

f After the phosphorus result at V2 is received from the central laboratory, a dose adjustment phone call at V2a (as soon as possible once V2 serum phosphorus is available) will be made by the investigator to instruct patients to adjust their starting IMP dosage, if dose adjustment is needed. The adjusted dose is 1 tablet (if serum phosphorus is $\leq$7.5 mg/dL at V2) or 2 tablets (if serum phosphorus is >7.5 mg/dL at V2) of Renvela or placebo 3 times per day (TID) with meals. A confirmation phone call (a second phone call, in addition to the dose adjustment phone call) will be made a working day after dose adjusting phone call, in order to remind patients their correct dosage.

g If dose titration is required, a dose titration phone call will be made by the investigator to patients as soon as possible once serum phosphorus result is available. A confirmation phone call (a second phone call, in addition to the dose titration phone call) will be made a working day after dose titration phone call (a total of two phone calls), in order to remind subjects their correct dosage. However, no phone calls will be required if dose titration is not required.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BP:	blood pressure
BUN:	blood urea nitrogen
CBC:	complete blood count
CFDA:	China Food and Drug Administration
CKD:	Chronic Kidney Disease
CKD-MBD:	Chronic Kidney Disease - Mineral and Bone Disorder
DBTP:	double blind treatment period
DRF:	Discrepancy Resolution Form
e-CRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EMA:	European Medicine Agency
GCP:	good clinical practice
GFR:	Glomerular Filtration Rate
HDL-C:	high-density lipoprotein cholesterol
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
IMP:	investigational medicinal product
iPTH:	intact parathyroid hormone
IVRS:	interactive voice response system
IWRS:	interactive web response system
KDIGO:	Kidney Disease Improving Global Outcomes
LDL-C:	low-density lipoprotein cholesterol
LLT:	lowest level term
LOCF:	Last Observation Carried Forward
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	Modified Intention To Treat
non-HDL-C:	non-high-density lipoprotein cholesterol
PCSA:	potentially clinically significant abnormality
PT:	preferred term
PTH:	parathyroid hormone
SAP:	statistical analysis plan
SD:	standard deviation
SOC:	system organ class
TEAE:	treatment emergent adverse event
TID:	3 times per day
ULN:	upper limit of normal range

4 INTRODUCTION AND RATIONALE

Chronic kidney disease (CKD) is a progressive disease in which over time the filtering capacity of the kidney gradually diminishes until renal replacement therapy is required. Based on a recently published, and also the first China cross-sectional survey, prevalence of CKD in China is 10.8%, which accounts for approximately 119.5 million patients (1). This estimated prevalence of CKD in China is similar to that reported for United States (10%) and Japan (13%) (2, 3). The Kidney Disease Improving Global Outcomes (KDIGO) recognizes the causal role of hyperphosphatemia and secondary hyperparathyroidism in Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), and its relation to increased morbidity and mortality (4). Hyperphosphatemia is an independent risk factor for cardiovascular mortality and all-cause mortality in CKD patients (5). Hyperphosphatemia directly stimulates parathyroid hormone (PTH) secretion. It also reduces serum calcium level, which in turn stimulates PTH secretion. High PTH reduces tubular reabsorption of phosphorus and returns serum phosphorus toward normal. It increases bone turnover, enhances bone resorption, and releases calcium and phosphorus into the circulation, causing hypercalcemia and aggravating hyperphosphatemia. High phosphate results in inhibition of 1E-hydroxylase and then contributing to vitamin D deficiency. In CKD, high PTH, high phosphorus, low calcium levels, and vitamin D deficiency are all part of the disturbed mineral metabolism that is a common complication of these patients.

CKD is classified (Stages 1-5) on the basis of the presence of kidney damage and the glomerular filtration rate (GFR). Hyperphosphatemia manifests prior to CKD Stage 5. Thus, there is an opportunity via phosphate binder therapy to provide therapeutic benefit to CKD patients prior to dialysis. The approach of identifying and treating early CKD is recommended by multiple clinical guidelines (4).

Renvela®, sevelamer carbonate, a non-absorbed, calcium free phosphate binder, is developed as a pharmaceutical alternate to sevelamer hydrochloride. Sevelamer carbonate is an anion exchange resin with the same polymeric structure as sevelamer hydrochloride where carbonate is an alternative counterion to chloride. Replacement of the counterion with carbonate provides alkali supplementation to CKD patients who typically develop metabolic acidosis as a result of underlying kidney insufficiency. While the counterions differ for the two salts, the polymer itself, the active moiety responsible for binding of phosphate, is the same.

The multiple groups in sevelamer carbonate become protonated in the stomach, and thus positively charged, and bind negatively charged ions in the intestine such as phosphate that are liberated during the digestive process. Phosphate sequestered by the polymer is not absorbed into the blood, but passes through the intestine and is excreted in the feces (4).

Renvela tablet is approved by China Food and Drug Administration (CFDA) in June 2013 to control hyperphosphatemia in CKD patients on dialysis based on SVCARB03808 study (6). This randomized, double-blind, dose-titration study compared Renvela with placebo over 8 weeks' duration in Chinese CKD patients on haemodialysis. Patients were required to be using calcium-based binders prior to study start. In all, 205 patients were randomized (Renvela, n = 135; placebo, n = 70). The mean serum phosphorus decreased significantly in patients treated with

Renvela (change -2.14 ±1.98 mg/dL) but remained persistently elevated with placebo (change -0.19 ±1.76 mg/dL, P <0.0001). When compared with placebo, Renvela treatment resulted in statistically significant greater mean reductions from baseline in serum total cholesterol (-17.1% versus -3.3%). Renvela was well tolerated with 96% adherence compared with 97% adherence in the placebo arm. Overall, adverse events experienced by patients in Renvela and placebo treatment groups were similar and consistent with their underlying renal disease.

In Europe, Renvela is approved to treat hyperphosphatemia in not-on-dialysis population based on SVCARB00105 (7). This was an open-label, dosage-titration study. Patients with serum phosphorus ≥5.5 mg/dL were enrolled (n = 46). Renvela was administered for 8 weeks. The primary efficacy parameter was the change from baseline in serum phosphorus. Renvela treatment resulted in a statistically significant decrease in mean serum phosphorus levels from baseline to end of treatment. A total of 75% of patients with CKD Stage 4 and 70% of patients with CKD Stage 5 achieved the target serum phosphorus (2.7 ~ 4.6 mg/dL) at the end of treatment. Sevelamer carbonate was well tolerated in this population.

Giving sevelamer's mode of action, Renvela should be taken three times a day with meals. No separate dose-response studies were performed with Renvela to be used in pre-dialysis CKD patients, or CKD patients on dialysis. The dose was based on the titrated dose of sevelamer hydrochloride obtained during the run-in period (GD3-163-201 and SVCARB00205) or the highest starting dose of sevelamer hydrochloride (GD3-199-301). The starting dose of sevelamer hydrochloride ranges from 2.4 g/day to 4.8 g/day, and is titrated at regular intervals based on serum phosphorus levels until an acceptable serum phosphorus level is reached (8). Based on totality of Renvela and sevelamer hydrochloride registration study data, the recommended starting dose of Renvela is 2.4 g/day to 4.8 g/day with meals depending on serum phosphorus level. With Renvela immediate effect on phosphorus absorption in intestine, it is expected that pharmacodynamic steady state is reached fairly quickly. In addition, hyperphosphatemia in CKD patients not on dialysis is not a therapeutic emergency. Considering both, it is decided to titrate dose with an interval of 2 weeks from administrative convenience aspect. In CKD patients on dialysis, the maximum dose studied was 14 g of Renvela as in United States and European Union label (9, 10). There is not yet approved drug covers not-on-dialysis population in China. This China registration study is designed to evaluate the benefits and risks of Renvela tablet to control hyperphosphatemia in CKD patients not on dialysis.

Patient population selection for this study is partially based on SVCARB00105. Therefore CKD patients not on dialysis with serum phosphorus ≥5.5 mg/dL are the target population (7). Target serum phosphorus level follows China Society of Nephrology recommendation (>4.5 mg/dL) (11). Due to a possible effect on the absorption of vitamin D, a fat-soluble vitamin, "patient with 25-hydroxy vitamin D ≥5 ng/mL" will be one of the eligibility criteria. In addition, previous studies had shown to have favorable effects on the lipid profile. Nevertheless, we endeavor patients continue their screening doses of lipid lowering medication, 1, 25-dihydroxy vitamin D, and/or cinacalcet for the duration of the study as in SVCARB00105 study.

Duration of screening is up to 4 weeks. For patients who are not taking phosphate binder(s) at screening visit, up to 10 days Screening Period is allowed for central laboratory to report serum phosphorus, intact parathyroid hormone (iPTH) and 25-hydroxy vitamin D levels. For the ones who are taking phosphate binder(s), a 2-week Washout is to allow effect of previous phosphate

binder(s) subside before testing baseline serum phosphorus. The 8-week Treatment Period is set to allow Renvela reaches stable and full serum phosphorus reduction (6, 7, 12, 13, 14, 15).

Evidence model utilized in KDIGO CKD–MBD Guideline regards serum phosphorus as an appropriate laboratory surrogate outcome (4). This viewpoint and precedence from European Medicine Agency (EMA) would support using serum phosphorus control as the primary endpoint.

Placebo is considered as an appropriate control as giving no phosphate binder is indicated to treat hyperphosphatemia in CKD pre-dialysis patients in China. Even calcium carbonate and calcium acetate are used in clinical as phosphate binders, there is no well-designed randomized control trials assessing carbonate phosphate binders' efficacy and safety in not-on-dialysis population. Calcium-based phosphate binders do not meet the requirement of a suitable active comparator treatment as indicated in ICH E9 Section 3.3.2 and ICH E10 2.4.1.

Objective of this study is to obtain new indication of Renvela in China. Per China regulation, efficacy and safety in a minimum of 200 Chinese patients (100 patients in each arm) is required. This gives a power of 90% for detecting a difference of 1 mg/dL in serum phosphorus. Based on recent meta-analysis of serum level of phosphorus and risk of death and cardiovascular disease in CKD population, all-cause mortality and cardiovascular mortality increased 18% and 10%, respectively, for every 1 mg/dL increase in serum phosphorus (5). This is hence considered clinically relevant.

5 STUDY OBJECTIVES

5.1 PRIMARY

- The primary objective of this study is to demonstrate efficacy of Renvela tablets in the reduction of serum phosphorus in hyperphosphatemia in patients with CKD not on dialysis.

5.2 SECONDARY

- To document the efficacy of Renvela tablets in the reduction of serum lipids (total cholesterol and low-density lipoprotein cholesterol [LDL-C]).
- To document the efficacy of Renvela tablets in the reduction of calcium-phosphorus product.
- To document the efficacy of Renvela tablets in the reduction of iPTH.
- To document the efficacy of Renvela tablets in proportion of patients reaching the target serum phosphorus level (4.6 mg/dL [1.49 mmol/L], inclusive).
- To evaluate safety of Renvela tablets.

6 STUDY DESIGN

This is a phase III, multi-center, randomized, double blind, placebo-controlled, balanced (1:1, Renvela:placebo), parallel-group study to evaluate the efficacy and safety of Renvela versus placebo in hyperphosphatemic CKD patients not on dialysis in China.

Eligible patients who are taking phosphate binder(s) at screening visit will enter a 2-week phosphate binder washout period before V1a. Eligible patients who are not taking phosphate binder(s) at screening visit will proceed directly to the start of the 8-week treatment period (Day 1).

Randomization will be stratified according to screening serum phosphorus (≥5.5 – 6.0 mg/dL [1.78 – 1.94 mmol/L] and >6.0 mg/dL [1.94 mmol/L]). For eligible patients who are not taking phosphate binder(s) at screening visit, serum phosphorus at V1 will be used for stratification. For eligible patients who are taking phosphate binder(s) at screening visit, serum phosphorus at V1a will be used for stratification. After randomization, patients will receive double-blind study treatment (either Renvela or placebo) over a period of 8 weeks.

Patients will be followed for 2 weeks after the last visit of the Double Blinded Treatment Period (DBTP).

6.1 DESCRIPTION OF THE PROTOCOL

The study consists of 3 periods: screening, double-blind treatment, and follow up.

- Screening period – up to 4 weeks in duration, including a washout period during which eligible patients who are taking phosphate binder(s) at screening visit will enter a 2-week phosphate binder washout period. Eligible patients who are not taking phosphate binder(s) at screening visit will proceed directly to the start of the 8-week treatment period as soon as possible once the central laboratory results are received (Day 1).
- Double-blind treatment period – A randomized, double-blind study treatment period of 8 weeks. The first administration of the investigational medicinal product (IMP) during the double-blind period will be done at the site on the day of randomization (Week 0 [D1] -V2) and as soon as possible after the contact with interactive voice response system (IVRS)/interactive web response system (IWRS) for randomization into the study.

  After randomization:

  - 1 (if serum phosphorus is between 5.5 – 7.5 mg/dL [inclusive] at screening) tablet of Renvela or placebo will be taken orally 3 times per day (TID) with meals

    or

  - 2 (if serum phosphorus is >7.5 mg/dL at screening) tablets of Renvela or placebo will be taken orally TID with meals.

For eligible patients who are not taking phosphate binder(s) at screening visit, serum phosphorus at V1 will be used for determination of the starting dose. For eligible patients who are taking phosphate binder(s) at screening visit, serum phosphorus at V1a will be used.

In order to adjust the deviation of starting dose based on phosphorus at screening, after the phosphorus result at V2 is received from the central laboratory, a dose adjustment phone call at V2a (as soon as possible once serum phosphorus at V2 is available) will be made by the investigator to instruct patients to adjust their IMP starting dose, if dose adjustment is needed. The adjusted dose at V2a is 1 tablet (if serum phosphorus is ≤7.5 mg/dL at V2) or 2 tablets (if serum phosphorus is >7.5 mg/dL at V2) of Renvela or placebo 3 times per day (TID) with meals.

During the Treatment Period, patients return to the investigative site every 2 weeks. Samples for laboratory measurements are collected at each site visit. After the results are received from the central laboratory, the serum phosphorus results are evaluated. Investigator will be informed by the IVRS/IWRS for dose titration. If the serum phosphorus is ≥4.6 mg/dL (≥1.49 mmol/L), the patient is to be instructed by the investigator to increase their study treatment dose by 1 tablet TID with meals. If the serum phosphorus is <2.7 mg/dL (<0.87 mmol/L), the patient is to be instructed by the investigator to decrease their study treatment dose by 1 tablet TID with meals.

- Post-treatment period – A period of 2 weeks after the end of the DBTP.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The study duration includes a screening period of up to 4 weeks, an 8-week DBTP for efficacy and safety assessment, and a 2-week post-treatment period for all patients after the last visit of the DBTP.

Thus, the study duration per patient is about 14 weeks (up to 4 weeks screening + 8 weeks DBTP + 2 weeks follow-up). The 2-weeks washout period is only applicable to eligible patients taking phosphate binder(s) at screening visit.

Patients who experience an ongoing SAE or an Adverse Event of Special Interest (AESI), at the pre-specified study end-date, should be followed until resolution, stabilization or death, and related data will be collected.

6.2.2 Determination of end of clinical trial (all patients)

The end of the study is defined as being the last patient last on site visit as scheduled by protocol.

6.3 INTERIM ANALYSIS

No interim analysis is planned.

6.4 STUDY COMMITTEE

The Steering Committee is composed of hospital-based clinicians (experts in the field of renal, and/or nephrologist) with clinical and methodological expertise, working in collaboration with Sponsor based scientists. The Steering Committee provides scientific opinions and advice related to the conduct, results analysis, and publication strategy for this study to Sanofi and investigators.

Among its responsibilities, the Steering Committee may/will review blinded study status reports from the Sponsor. The Steering Committee members and Sponsor based scientists will participate in face-to-face meetings at regular intervals throughout the study and/or in regularly scheduled teleconferences.

Detailed activities and responsibilities of the Steering Committee are described in the Steering Committee charter.

7 SELECTION OF PATIENTS

Chronic kidney disease has been defined according to the criteria:

1. Kidney damage ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either:

- Pathological abnormalities; or
- Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests.

2. GFR <60 mL/min/1.73 m^2 for ≥3 months, with or without kidney damage.

7.1 INCLUSION CRITERIA

I 01. Patients with CKD who have not been on dialysis, and are not expected to begin dialysis, or renal transplantation in the next 4 months from the Screening Visit.

I 02. Have serum phosphorus measurement ≥5.5 mg/dL (1.78 mmol/L) at Screening Visit (if patients are not on phosphate binder[s] at Screening Visit) OR at the end of Washout Period (if patients are on phosphate binder[s] at Screening Visit).

I 03. Have the following laboratory measurements at Screening Visit:

- 25-hydroxy vitamin D ≥5 ng/mL
- iPTH ≤800 pg/mL.

I 04. Signed written informed consent.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 4 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Men or women below 18 years of age.

E 02. Any technical/administrative reason that makes it impossible to randomize the patient in the study.

E 03. Is not of the level of understanding and willingness to cooperate with all visits and procedures, as described in the study protocol.

E 04. Not yet received CKD diet education before Screening Visit.

E 05. Not willing and not able to avoid changes to diet during the study.

E 06. Not willing or not able to maintain screening doses of lipid lowering medication, 1, 25 dihydroxy vitamin D, and/or cinacalcet for the duration of the study, except for safety reasons.

E 07. Not willing or not able to avoid antacids and phosphate binders containing aluminium, magnesium, calcium or lanthanum for the duration of the study unless prescribed as an evening calcium supplement.

E 08. Have participated in any other investigational drug studies within 30 days or 5 half-lives, whichever is longer, prior to Screening Visit.

E 09. Conditions/situations such as:

- Patient is the Investigator or any Subinvestigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.
- Uncooperative or any condition that could make the patient potentially non-compliant to the study procedures (for example, patients cannot be contacted by phones as required in phone call visits).
- Evidence of active malignancy.
- Not on stable medical condition (for example, but not limited to, active ethanol or drug abuse [tobacco use acceptable]; documented poorly controlled diabetes mellitus, poorly controlled hypertension, active vasculitis, HIV infection), or has any clinically significant medical conditions.

7.2.2 Exclusion criteria related to the current knowledge of Sanofi compound

E 10. Have known hypersensitivity to sevelamer or any constituents of Renvela tablets.

E 11. Have bowel obstruction, active dysphagia, swallowing disorder, a predisposition to or current bowel obstruction, ileus, or severe gastrointestinal motility disorders including severe constipation.

E 12. Using or plan to use anti-arrhythmic or anti-seizure medications for arrhythmia or seizure disorders.

E 13. Is pregnant or breast-feeding.

E 14. If the patient is female, and of childbearing potential (such as pre-menopausal and not surgically sterile, postmenopausal women who are amenorrheic for less than12 months), is not willing to use an effective contraceptive method throughout the study.

E 15. Have any condition, which in the opinion of the investigator would prohibit the patient's inclusion in the study.

7.2.3 Additional exclusion criteria during or at the end of screening or washout period before randomization

E 16. Patient who has withdrawn consent before randomization (starting from signed informed consent form).

E 17. Have serum phosphorus measurement <5.5 mg/dL (1.78 mmol/L) at Screening Visit (if patients are not on phosphate binder[s] at Screening Visit) **OR** at the end of Washout Period (if patients are on phosphate binder[s] at Screening Visit).

Re-screening:

Patients who are screened and failed to fulfill the inclusion or exclusion criteria could be re-screened if their screening central lab results are as follows:

- serum phosphorus levels >4.6 mg/dL (1.49 mmol/L)

Re-screen is not advised within 1 month of the prior screening attempt. All patients re-screened must sign a consent form prior to any re-screening activities taking place. The number of re-screening attempts will be limited to two. Careful consideration is necessary as to the appropriateness of multiple re-screening attempts. Patients should only be re-screened if their condition has progressed such that the treating physician believes that they may now be eligible and the patient is a willing participant. Patients who fail screening following wash out from their usual phosphate binder(s) may be prescribed these again at the physician's discretion. However the dose should be considered to be stabilized by the investigator prior to re-screening.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Investigational medicinal product is either Renvela or placebo for Renvela. Renvela (sevelamer carbonate) is chemically known as poly (allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane), carbonate salt. It is a polymeric anion exchange resin where the amines in the polymer exist in a protonated form and bind to negatively charged phosphates. The 800 mg tablet contains the active ingredient sevelamer carbonate and the inactive ingredients are hypromellose, diacetylated monoglyceride, microcrystalline cellulose, zinc stearate, and sodium chloride. Renvela or placebo for Renvela will be supplied as a white to off white tablet with no imprinting. Sevelamer carbonate tablets and/or matching placebo tablets (IMP) will be supplied in bottles containing 180 tablets.

All study medication will be taken orally three times per day with meals from randomization visit to end of treatment visit (8 weeks in total). Sufficient liquid should be taken to ensure the tablets clear the oral cavity and esophagus. Patients will be instructed not to bite, chew, mix with food, or dissolve tablets in water prior to dosing. Patients will be instructed to take the study medication with meal. One to five tablets of IMP taken orally three times per day with meals as directed by physician titrated to reach a target goal of serum phosphorus ≤4.6 mg/dL (≤1.49 mmol/L). Please refer to Section 6.1 for dose titration. The potential maximal dose could be up to 15 tablets a day.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Native vitamin D will be supplied by the Sponsor centrally as the noninvestigational medicinal product (NIMP). Patients will be supplemented with a daily dose of 400 IU of native vitamin D to be taken orally by drops at bedtime to minimize the effects of dietary absorption of vitamin D that may occur with treatment of sevelamer carbonate.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

Renvela and placebo for Renvela will be provided in identically matched tablet and packaged identically which includes labeling to protect the blind.

Each double-blind treatment kit will be labeled with treatment kit number. The treatment kit numbers will be obtained by the Investigator at the time of patient randomization and subsequent patient visits scheduled via the IVRS/IWRS that will be available 24 hours-a-day, 7 days-a-week.

In accordance with the double-blind design, study patients, Investigators and study site personnel will remain blinded to study treatment and will not have access to the randomization (treatment codes) except under circumstances described in Section 8.3.2.

8.3.2 Randomization code breaking during the study

In case of an adverse event (AE), the code should only be broken in circumstances when knowledge of the IMP is required for treating the patient. If possible, a contact should be initiated with the Monitoring Team/Medical Monitor before breaking the code. All calls will be documented by the Monitoring Team as appropriate to include date and time of the call, name of the person contacted within the Monitoring Team, patient identification, documentation of the request, and decision for unblinding or not.

Code breaking can be performed at any time by using the proper module of the IVRS/IWRS and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of day, reason for code breaking and report this information (or "relevant information as required by") on the appropriate page of the electronic-Case Report Form (e-CRF).

Note that when documenting the reason for unblinding, the Investigator must not provide any detail regarding the nature of the IMP. The Investigator should not divulge IMP detail to the Sponsor's representative or to any staff members until database closure. Furthermore, when completing forms (eg, AEs, SAEs), the study treatment should not be disclosed on the forms.

The code-breaking can also be performed by contacting the "24 hour alert system"; but this system should be used in very exceptional cases only (ie, unavailability of a centralized treatment allocation system or inability to contact Investigator and/or site staff). However, the preferred option is to unblind using a centralized treatment allocation system. The Investigators will be informed by the clinical monitoring team about the availability of the local code-breaking details (through an emergency centralized 24 hour telephone system for use with emergency scientific and medical services [e-SMS]). A patient card, including the relevant "24 hour alert system" telephone number will be provided to every patient who will participate in the study.

Unblinding may also be performed by the Sponsor for some SAEs that are both related and unexpected in order to conform to regulatory reporting requirements.

If the code is broken, the patient must withdraw from IMP administration.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The randomized treatment kit number list is generated centrally by Sanofi. The IMPs (Renvela or placebo kit) are packaged in accordance with this list. Both the randomization and treatment kit lists will be loaded into the centralized treatment allocation system.

Patients will be randomized to receive either placebo or Renvela during the double-blind study treatment period using a ratio 1:1. Randomization will be stratified according to screening serum phosphorus level [≥5.5 - 6.0 mg/dL or >6.0 mg/dL]. For eligible patients who are not taking phosphate binder(s) at screening visit, serum phosphorus at V1 will be used for stratification. For eligible patients who are taking phosphate binder(s) at screening visit, serum phosphorus at V1a will be used for stratification.

The treatment kit numbers will be allocated using the IVRS/IWRS on randomization visit (Day 1, Week 0), and then at Week 2, Week 4 and Week 6 as resupply visits, and at unscheduled visits, if needed.

Before randomizing a patient, the Investigator or designee will have to contact the IVRS/IWRS.

A randomized patient is defined as a patient who is registered and assigned with a treatment kit number from the IVRS/IWRS, as documented from its log file. A patient cannot be randomized more than once in the study. If a treatment is used without contacting the IVRS/IWRS patient will be considered as not randomized and withdrawn from the study.

Two types of centralized treatment allocation system will be used, the IVRS and the IWRS, depending on the choice of the site.

Details of the IVRS/IWRS procedures will be provided to sites in the IVRS/IWRS site manual.

8.5 PACKAGING AND LABELING

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

In order to protect the blind, IMP kits will have the same look and therefore will be labeled with a double-blind label.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of IMP storage conditions, especially control of temperature and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator’s prescription and it is the Investigator’s responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

IMP administration data will be recorded by the patients onto a patient's diary.

Measures taken to ensure and document IMP compliance and accountability are described below:

- The Investigator or designee will obtain via IVRS/IWRS the treatment kit numbers and he/she will dispense the treatment kits to the patient.
- The accountability is to be performed at Visits 3, 4, 5 and 6 (Days 15, 29, 43 and 57). The unused treatment should be returned by the patient to such visits for accountability purposes.
- The Investigator or designee will complete the corresponding treatment log form from patient's diary.
- The Investigator/study coordinator will enter data in the appropriate e-CRF pages, according to data recorded in the treatment log form.
- The monitor will check the data consistency between e-CRF pages, treatment log forms using patient's diary, and returned unused treatment.

8.7.2 Return and/or destruction of treatments

All partially used or unused treatment kits will be retrieved by the Sponsor or destroyed at study site. A detailed treatment log of the returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy the unused IMP unless the Sponsor provides written authorization.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to the study (from Screening Visit until Follow-Up visit).

All medications taken by the patient within 30 days of Screening Visit until study completion will be recorded in the patient's e-CRF. Patients will not consume calcium, aluminum, or magnesium containing antacids and phosphate binders throughout the duration of the study unless prescribed as an evening calcium supplement.

Should serum calcium (adjusted for albumin) fall below normal during the study, the investigator will return the serum calcium (adjusted for albumin) level to within the normal range by prescribing an evening calcium supplement to be taken at bedtime.

If the patient is on lipid lowering medication, 1, 25 dihydroxy Vitamin D, and/or cinacalcet therapy, the investigator will maintain the patient on the dose recorded at Screening Visit for the duration of the study, except for safety reasons.

To minimize the effects of dietary absorption of vitamin D that may occur with treatment with sevelamer carbonate, patients will be supplemented with a daily dose of 400 IU of the native form of this vitamin to be taken at bedtime away from the dose of sevelamer carbonate. This supplement should be given in addition to any ongoing active vitamin D therapy routinely prescribed.

8.8.1 Prohibited concomitant medications

Forbidden concomitant medications from the initial Screening Visit until the Follow-Up visit include the following:

- Anti-arrhythmic and anti-epileptics for arrhythmia or seizure disorders.
- Antacids and phosphate binders containing aluminium, magnesium, calcium or lanthanum for the duration of the study unless prescribed as an evening calcium supplement.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

The primary endpoint is the change from baseline in serum phosphorus level at Week 8.

The baseline of serum phosphorus value will be the last serum phosphorus level obtained before the first double-blind IMP dosing.

The serum phosphorus at Week 8 will be the serum phosphorus level obtained within the Week 8 analysis window.

All serum phosphorus values (scheduled or unscheduled) may be used to provide a value for the primary endpoint if appropriate according to above definition. The analysis window used to allocate a time point to a measurement will be defined in the Statistical Analysis Plan (SAP).

9.2 SECONDARY ENDPOINTS

- The change from baseline in total cholesterol at Week 8
- The change from baseline in LDL-C at Week 8
- The change from baseline in calcium-phosphorus product at Week 8
- The change from baseline in iPTH level at Week 8
- Percentage of patients reaching the target serum phosphorus level (4.6 mg/dL [1.49 mmol/L], inclusive) at Week 8
- The change from baseline in serum phosphorus level at Week 4

9.3 SAFETY ENDPOINTS

- Proportion of patients with adverse events
- Clinically significant changes in vital signs and clinical laboratory parameters

Observation period

The observation of safety data will be as follows:

- Pre-treatment period: The pre-treatment observation period is defined from the signed informed consent up to the first dose of double-blind IMP.
- Treatment Emergent Adverse Event (TEAE) period: The TEAE observation period is defined as the time from the first dose of double-blind IMP to the last dose of double-blind IMP+3 days.

- Post-treatment period: The post-treatment observation period is defined as the time starting the day after the end of the TEAE period up to the end of the study (see definition in Section 6.2.1).

9.3.1 Adverse events

All AEs diagnosed by the Investigator will be reported and described.

All AEs will be coded to a "Lowest level term (LLT)", "Preferred term (PT)", "High level term (HLT)", "High level group term (HLGT)" and associated primary "System organ class (SOC)" using the version of Medical dictionary for regulatory activities (MedDRA) currently at Sanofi at the time of the considered database lock.

Refer to Section 10.4 to Section 10.7 for details.

9.3.2 Laboratory safety variables

The clinical laboratory data consist of hematology (complete blood count [CBC], differential, platelet and prothrombin time), chemistry (serum phosphorus, calcium [adjusted for albumin], albumin, calcium-phosphorus product, chloride, bicarbonate, uric acid, sodium, potassium, glucose, blood urea nitrogen [BUN], alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine), and lipid panel (total cholesterol, LDL-C, high-density lipoprotein cholesterol [HDL-C], non-high-density lipoprotein cholesterol [non-HDL-C] and triglycerides).

Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

9.3.3 Vital signs

Vital signs include: heart rate (HR), systolic blood pressure (BP) and diastolic BP, and body temperature in sitting position.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

For all visits after Day 1/Week 0 (randomization visit), a timeframe of ±3 days will be allowed.

For all visits after Day 1/Week 0 (randomization visit), if one visit date is changed, then the next visit should take place according to the original schedule as outlined Section 1.2.

Laboratory tests:

The laboratory data are collected in accordance with the study schedule in Section 1.2:

- Hematology
- Chemistry
- Serum pregnancy test

NOTE: Any clinically relevant abnormal laboratory value should be immediately rechecked for confirmation before making any decision for the concerned patient. It should be documented as an AE/SAE as applicable. Please also refer to Section 10.4.

According to the discretion of the Investigator for safety concern, the relevant laboratory parameters (eg, serum potassium) can be tested at any scheduled visit or unscheduled visit if necessary.

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix A.

Physical examination:

A general physical examination should be performed at the time points indicated in the study flowchart in Section 1.2. If a new clinically significant abnormality or worsening from baseline is detected after randomization, then an AE should be reported and the patient should be considered for further clinical investigations and/or specialist consultation as per the Investigator's medical judgment.

Blood pressure / heart rate:

Blood pressure should be measured in sitting position under standardized conditions, approximately at the same time of the day, on the same arm, with the same apparatus (after the patient has rested comfortably in sitting position for at least five minutes). Values are to be recorded in the e-CRF; both systolic BP and diastolic BP should be recorded. At the first Screening Visit, BP should be measured in both arms. The arm with the highest diastolic pressure will be determined at this visit, and BP should be measured on this arm throughout the study. This highest value will be recorded in the e-CRF.

Heart rate will be measured at the time of the measurement of BP.

NOTE: in case of high BP values at Screening Visit, the Investigator is responsible for the optimization of the patient's treatment to achieve BP targets as defined by local guidelines.

Body weight and height

Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study.

The use of calibrated balance scales is recommended, if possible. Self-reported weights are not acceptable; patients must not read the scales themselves.

Height needs to be measured as self-reported heights are not acceptable.

10.1.1 Screening Period

The screening period will take place up to 4 weeks or 28 days (and as short as possible, upon receipt of laboratory eligibility criteria) prior to randomization/Day 1 visit. Eligible patients who are taking phosphate binder(s) at Screening Visit will enter a 2-week phosphate binder washout period. Eligible patients who are not taking phosphate binder(s) at screening visit will proceed to the start of the 8-week treatment period (Day 1).

10.1.1.1 Screening Visit (Visit 1/Week -4 /Day -28 up to -19 for patients on phosphate binder[s] and Visit 1/Week -1.5/Day -10 to -1 for patients not on phosphate binder[s])

- Complete informed consent - the patient will receive complete information about the study both verbally and in writing. Written informed consent for the study must be obtained prior to any study-related investigations.
- Assess inclusion/exclusion criteria.
- Obtain patient demography – age and gender.
- Obtain medical history (including menopausal status) and renal history.
- Document prior medication (prescription and non-prescription medication) history within the last 30 days, especially for phosphate binder(s) treatment.
- Record concomitant medication (prescription and non-prescription medication).
- Physical examination.
- Take vital signs including HR, BP and body temperature.
- Get body weight and height measurements.
- Contact IVRS/IWRS for notification of Screening Visit. Patient number will be allocated by the IVRS/IWRS. This patient number is composed of a 12-digit number containing the 3-digit country code, the 4-digit center code and the 5-digit patient chronological number

(the 5-digit patient chronological number is 00001 for the first patient screened in a center, 00002 for the second patient screened in the same center).

- Collect AEs from this point onward:

All AEs and SAEs will be collected from the time of informed consent signature and throughout the study until the post Follow-Up visit.

- Obtain blood sample for:
  - Hematology: CBC, differential, platelet and prothrombin time.
  - Chemistry: calcium (adjusted for albumin), albumin, calcium-phosphorus product, chloride, bicarbonate and creatinine.
  - Serum phosphorus.
  - Serum iPTH.
  - Serum 25-hydroxy vitamin D.
  - Serum pregnancy test (women of childbearing potential only).
  - Calculate and record estimated Glomerular Filtration Rate (eGFR) based upon screening values using Modification of Diet in Renal Disease (MDRD) formula:

    eGFR (mL/min/1.73 m^2) = 175 x (serum creatinine [mg/dL])$^{-1.154}$ x (Age [years])$^{-0.203}$ x (0.742, if female)
- Inform patient who are taking phosphate binder(s) to discontinue their current phosphate binder(s) for 2 weeks (washout period). These patients will return for their V1a (Day -10 to -1).
- An appointment will be given for the next visit.

10.1.1.2 Post-Washout visit (Visit 1a/Week -1.5/Day -10 to -1)

This visit is only applied for patients taking phosphate binder(s) at screening visit.

- Assess inclusion/exclusion criteria.
- Collect AEs.
- Record concomitant medication (prescription and non-prescription medication).
- Obtain blood sample for:
  - Chemistry: serum phosphorus.
- An appointment will be given for the next visit.

Note: For patients on phosphate binder(s), the time window of V1 and V1a is up to 10 days, respectively. However, the total time window of V1 and V1a should not exceed 14 days to ensure the screening period is up to 4 weeks, including a wash out period which should be 2 weeks (14 days).

10.1.2 Double-Blind Treatment Period (Study Site Visits)

10.1.2.1 Randomization Visit (Visit 2/Week 0/Day 1)

- Assess Inclusion/Exclusion Criteria.
- Physical examination.
- Take vital signs including HR, BP and body temperature.
- Get body weight measurements.
- Collect AEs.
- Record concomitant medication (prescription and non-prescription medication).
- Obtain blood sample for:
  - Hematology: CBC, differential, platelet and prothrombin time.
  - Chemistry: calcium (adjusted for albumin), albumin, calcium-phosphorus product, chloride, bicarbonate, uric acid, sodium, potassium, glucose, BUN, liver function tests (ALT and AST), creatinine.
  - Serum phosphorus.
  - Lipid panel: total cholesterol, LDL-C, HDL-C, non-HDL-C and triglycerides.
  - Serum iPTH.
- If the patient is confirmed eligible, the Investigator will start the next study procedures:
  - IVRS/IWRS contact for randomization and allocation of a 7-digit treatment kit numbers according to the randomization list. Investigators should never allocate a treatment kit number to a patient without contacting IVRS/IWRS.
- Double-blind IMP kits dispensation as per treatment kit numbers provided by IVRS/IWRS along with schedule reminder.
- The first double-blind IMP administration will take place at the study site, but only after the collection of the blood samples and after the assessment of all evaluations planned at that visit.
- Instruct the patient to maintain the prescribed dose of IMP including taking daily dose of 400 IU of native vitamin D.
- The patient diary should be given and instructions on its completion should be reviewed.
- Reminders
  - An appointment will be given for the next study site visit.
  - Patient to bring the diary, at the next study site visit.
  - Patient to bring unused treatment at the next study site visit.

10.1.2.2 Visit 2a: Phone Call Visit

After the phosphorus result at V2 is received from the central laboratory, a dose adjustment phone call at V2a (as soon as possible once V2 serum phosphorus is available) will be made by the investigator to instruct patients to adjust their starting IMP dosage, if dose adjustment is needed. The adjusted dose is 1 tablet (if serum phosphorus is ≤7.5 mg/dL at V2) or 2 tablets (if serum phosphorus is >7.5 mg/dL at V2) of Renvela or placebo 3 times per day (TID) with meals. A confirmation phone call (a second phone call, in addition to the dose adjustment phone call) will be made a working day after dose adjusting phone call, in order to remind patients their correct dosage.

10.1.2.3 Visit 3/Week 2, Visit 4/Week 4 and Visit 5/Week 6 (Day 15, 29 and 43 ± 3)

- Physical examination.
- Take vital signs including HR, BP and body temperature.
- Get body weight measurements.
- Collect AEs.
- Record concomitant medication (prescription and non-prescription medication.
- Data collection on IMP administration and IMP compliance check by review of diary and unused treatment.
- Obtain blood sample for:
  - Chemistry: calcium (adjusted for albumin), albumin, calcium-phosphorus product, chloride, and bicarbonate.
  - Serum phosphorus.
  - Serum iPTH.
- Return the bottle (s) and any unused treatment to the site; dispense enough additional IMP for 2 weeks treatment.
- Instruct the patient to maintain the prescribed dose of IMP including taking daily dose of 400 IU of native vitamin D.
- Once the central laboratory results are available for Visit 3, 4 and 5, Investigator will be informed by the IVRS/IWRS for dose titration. If the serum phosphorus is ≥4.6 mg/dL (≥1.49 mmol/L), the patient is to be instructed by the investigator to increase their study treatment dose by 1 x 800 mg tablet TID with meals. If the serum phosphorus is <2.7 mg/dL (<0.87 mmol/L), the patient is to be instructed by the investigator to decrease their study treatment dose by 1 x 800 mg tablet TID with meals.
- Reminders
  - An appointment will be given for the next study site visit.
  - Patient to bring the diary at the next study site visit.
  - Patient to bring unused treatment at the next study site visit.

10.1.2.4 Visit 3a/Visit 4a/Visit 5a: Phone Call Visits

- If dose titration is required, a dose titration phone call will be made by the investigator to patients as soon as possible once serum phosphorus result is available. A confirmation phone call (a second phone call, in addition to the dose titration phone call) will be made a working day after dose titration phone call, in order to remind subjects their correct dosage.
- Instruct the patient to maintain the prescribed dose of IMP including taking daily dose of 400 IU of native vitamin D.

10.1.2.5 Visit 6/Week 8 (Day 57 ± 3): End of Treatment Visit

- Physical examination.
- Take vital signs including HR, BP and body temperature.
- Get body weight measurements.
- Collect AEs.
- Record concomitant medication (prescription and non-prescription medication).
- IVRS/IWRS contact to document the end of treatment.
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit accountability.
- Obtain blood sample for:
  - Hematology: CBC, differential, platelet and prothrombin time.
  - Chemistry: calcium (adjusted for albumin), albumin, calcium-phosphorus product, chloride, bicarbonate, uric acid, sodium, potassium, glucose, BUN, liver function tests (ALT and AST), creatinine.
  - Serum phosphorus.
  - Lipid panel: total cholesterol, LDL-C, HDL-C, non-HDL-C and triglycerides.
  - Serum iPTH.
- Instruct patients to refrain from taking any phosphate binder(s).
- Reminders
  - An appointment will be given for the next study site visit.

10.1.3 Post-Treatment Period

10.1.3.1 Follow-Up Visit (Visit 7/ Week 10/ Day 71 ± 3)

- Collect AEs.
- Record concomitant medication (prescription and non-prescription medication).
- IVRS/IWRS contact to document the end of study.
- Instruct patients to return to their previous phosphate binder(s) (if applicable).

- Obtain blood sample for:

  Only in case of clinically relevant abnormal values for these parameters at the end of treatment visit will the following be obtained at this visit:

  - Hematology: CBC, differential, platelet and prothrombin time.
  - Chemistry: calcium (adjusted for albumin), albumin, calcium-phosphorus product, chloride, bicarbonate, uric acid, sodium, potassium, glucose, BUN, liver function tests (ALT and AST), creatinine.
  - Serum phosphorus.
  - Lipid panel: total cholesterol, LDL-C, HDL-C, non-HDL-C and triglycerides.

10.2 DEFINITION OF SOURCE DATA

Evaluations that are reported in the e-CRF must be supported by appropriately signed identified source documentation related but not limited to the following:

- Agreement, date, and signature of informed consent mentioning the study identification.
- Patient identification, last participation in a clinical trial, medical history, associated diseases, and data related to the studied pathology.
- Contraception methods for women of childbearing potential.
- Previous and concomitant medication.
- Study identification.
- Treatment number, dates of administration.
- Dates of visits and assessments including the examination report.
- Vital signs, height, body weight.
- Emailed central lab reports (dated and signed by the Principal Investigator or Subinvestigator).
- IVRS/IWRS confirmation email (screening, screen failure, training kit allocation, randomization, treatment reallocation, discontinuation, end of DBTP, end of study, unblinding if applicable).
- AEs and follow-up:
  - In case of SAE, the site should file in the source document at least copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the SAE.
- Date of premature study discontinuation (if any) and reason.

Source documentation may be found in the following:

- Patient’s identity.
- Medical history.
- Hospital records.
- Nursing notes.
- Physician’s notes.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the e-CRF. In any case, the patient should remain in the study as long as possible.

- Pregnancy in female participant will lead to definitive treatment discontinuation in all cases.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Reinitiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2).

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator’s decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

Patients should discontinue the IMP for the following reasons:

- Pregnancy, intention for pregnancy, or no longer with effective contraceptive method of birth control (females only).
- Serious adverse event (or non-serious but severe in intensity) of hypersensitivity reaction considered related to IMP.
- At patient request.
- If, in the Investigator's opinion, continuation with the administration of the IMP would be detrimental to the patient's well-being.
- Intercurrent condition that requires discontinuation of the IMP (eg, laboratory abnormalities, please refer to decision tree Appendix A).

- At the specific request of the Sponsor.
- Any code breaking requested by the Investigator.
- Patient receives double-blind treatment prior to randomization.

In addition, if the patient requires dialysis (hemodialysis or peritoneal dialysis) or is admitted for renal transplantation at any time, he or she must be withdrawn.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the IMP.

If applicable, instruct patient to resume their previous phosphate binder(s).

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed. The investigator will retrieve any unused treatment and instruct the patient to resume their phosphate binder(s), if applicable.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. If possible, the patients are assessed using the procedure normally planned for the end-of-study visit.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records (with, in this medical records, at least date of withdrawal and reason for) when considered as confirmed.

For patients who fail to return to the site, the Investigator should make the best effort to recontact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

Patients who have withdrawn from the study cannot be rerandomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or

  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:

a) Allergic bronchospasm

b) Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),

c) Convulsions (seizures, epilepsy, epileptic fit, absence seizures, etc).

- Development of drug dependence or drug abuse
- ALT >3 x upper limit of normal range (ULN) + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN

- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the Investigators in oncology studies)
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

10.4.1.3 Adverse event of special interest

An AESI is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment. Please see Section 10.4.4 and Appendix A for additional information.

- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP
  - Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2)
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or non-serious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count). Renvela is a non-absorbed drug, thus it is not possible to define a symptomatic overdose prospectively. However, the investigator may use his or her judgment to report an event that he or she considers to be a symptomatic overdose using the corresponding screens in the e-CRF using the Term "Symptomatic OVERDOSE (accidental [or intentional])". The patient should be monitored and appropriate symptomatic treatment instituted.

    The circumstances of the overdose should be clearly specified in the verbatim.

    Of note, asymptomatic overdose has to be reported as a standard AE.
- Increase in alanine transaminase (ALT) (see the "Increase in ALT" flow chart in Appendix A of the protocol).

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the e-CRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory or vital signs abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI

  Instructions for AE reporting are summarized in Table 1.

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team

within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.

- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.4 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF.

Instructions for AE reporting are summarized in Table 1.

10.4.5 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix A.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia
- Thrombocytopenia
- Suspicion of rhabdomyolysis
- Increase in ALT

NOTE: Increase in ALT can be considered as AESIs (see Section 10.4.1.3)

Table 1 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Pregnancy	Yes	Yes	Yes
		Symptomatic overdose	Yes	Yes	No
		ALT≥3 ULN (if baseline ALT<ULN) and ALT≥2 x baseline (if baseline ALT≥ULN)	Yes	Yes	Yes

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected (please refer to the IB).

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 SAFETY INSTRUCTIONS

- No specific safety instructions required in relation to the clinical trial.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size calculations are based on the primary efficacy variable of serum phosphorus change from baseline to Week 8, with the following assumptions:

- A common standard deviation (SD) of 2 mg/dL, which is assumed based on the data from previous trials
- A 1 mg/dL mean difference between test and placebo in change from baseline in serum phosphorus
- A t-test at a 2-sided 5% significance level with 90% power
- Expected dropout rate = 15%.

Based on the above assumptions, 101 patients per arm are needed for this study. Calculations were made using nQuery Advisor 7.0.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who met the inclusion criteria and signed the informed consent.

Randomized patients consist of all patients, who have been allocated a treatment kit by IVRS/IWRS, and regardless of whether the treatment kit was used or not.

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Modified intent-to-treat population

Modified Intention To Treat (mITT) population: The mITT population consists of all patients who are randomized, receive at least one dose of IMP, and have both a baseline assessment and at least one post-baseline assessment of phosphorus measure.

11.3.2 Safety population

Safety population: The safety population consists of all randomized patients who receive at least one dose of IMP.

In addition:

- Nonrandomized but treated patients with IMP will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For patients receiving more than 1 study treatment during the trial, the treatment group allocation for as-treated analysis will be in Renvela group.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

11.4.1.1 Extent of investigational medicinal product exposure

Duration of IMP exposure is defined as: last dose date – first dose date + 1 day, regardless of unplanned intermittent discontinuations.

11.4.1.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Treatment compliance, average dose, final dose and highest dose will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance is <80% will be summarized. In addition, number and percentage of patients with at least 1 above-planned dosing administration will be given, as well as the number and percentage of patients with 0, (0, 20%], and >20% under-planned dosing administrations.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint(s)

The change from baseline in serum phosphorus at Week 8 as defined in Section 9.1 will be compared between the Renvela group to the placebo group in the mITT population using stratified Wilcoxon rank sum tests considering randomization strata (screening serum phosphorus [≥5.5 - 6.0 mg/dL or >6.0 mg/dL]). The statistical test will be two-sided tests at a nominal 5% significance level.

If a patient discontinues the treatment prematurely or does not have serum phosphorus value at Week 8, the last post-baseline on-treatment serum phosphorus measurement during the 8-week double-blind period will be used for the calculation of Week 8 (Last Observation Carried Forward [LOCF] procedure).

11.4.2.2 Analyses of secondary efficacy endpoints

The secondary efficacy variables are:

- The change from baseline in total cholesterol at Week 8
- The change from baseline in LDL-C at Week 8
- The change from baseline in calcium-phosphorus product at Week 8
- The change from baseline in iPTH level at Week 8
- Percentage of patients reaching the target serum phosphorus level (4.6 mg/dL [1.49 mmol/L], inclusive) at Week 8
- The change from baseline in serum phosphorus level at Week 4

All secondary endpoints will be analyzed using the mITT population.

Descriptive statistics (number, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided by treatment for all continuous secondary variables at the scheduled visits.

All continuous secondary efficacy variables, ie, the change from baseline in serum lipids (total cholesterol and LDL-C), calcium-phosphorus product at Week 8, iPTH at Week 8 and serum phosphorus at Week 4 will be analyzed using stratified Wilcoxon rank sum tests using randomization strata (screening serum phosphorus [≥5.5 – 6.0 mg/dL or >6.0 mg/dL]), the same test described in Section 11.4.2.1. The same procedure for handling missing assessments/early discontinuation will also be applied as for the primary variable.

Percentage of patients reaching the target serum phosphorus level will be compared by treatment assignment (Renvela or placebo) using a Cochran-Mantel-Haensel method stratified by randomization strata (screening serum phosphorus [≥5.5 – 6.0 mg/dL or >6.0 mg/dL]), the odds ratio and 95% confidence intervals will be calculated.

11.4.2.3 Multiplicity considerations

In order to handle multiple key endpoints, the overall type-I error will be controlled by the use of a fixed sequence approach. Statistical significance of the primary parameter at the 0.05 alpha level is required before drawing inferential conclusions about first secondary endpoint (refer to order of list in Section 9.2). Inferential conclusions about successive secondary endpoints require statistical significance of the prior one.

This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the 0.05 level.

No further adjustments will be made for other secondary endpoints, for which p-values will be provided for descriptive purpose only (no claim).

11.4.3 Analyses of safety data

The summary of safety results will be presented by treatment group. No formal inferential testing will be performed. Summaries will be descriptive in nature.

All safety analyses will be performed on the Safety population using the following common rules:

- The baseline value is defined generally as the last available value before first dose administration.

The following definitions will be applied to laboratory parameters and vital signs.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs.
- PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

The observation period will be divided into three segments: pre-treatment, on-treatment and post-treatment

- The pre-treatment period is defined as the time between the date of the informed consent and the start of study medication.
- The on-treatment period is defined as the time from the first dose of study medication up to 3 days after the last dose of study medication administration.
- The post-treatment period is defined as the time starting 4 days after last dose of study medication administration (after the on-treatment period) to the end of the study.

11.4.3.1 Adverse events

Adverse event incidence tables will present by SOC (sorted by internationally agreed order), HLGT, HLT and PT sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment emergent AESI (defined with a PT or a prespecified grouping), all treatment emergent SAEs and all TEAEs leading to permanent treatment discontinuation.

Death:

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population by treatment received.
- Death in nonrandomized patients or randomized and not treated patients.
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC , HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

11.4.3.2 Laboratory data and vital signs

The summary statistics of all laboratory variables, all vital signs parameters will be calculated for each visit, and last value assessed during the treatment period and presented by treatment group.

The incidence of PCSAs at any time during the TEAE period (on-treatment PCSAs) will be summarized by treatment group whatever the baseline level and/or according to the following baseline categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For laboratory parameters for which PCSA criterion is not defined, similar table(s) using the normal range could be provided.

11.5 INTERIM ANALYSIS

No interim analysis is planned.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Subinvestigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

The informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

12.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator’s Brochure, Investigator’s curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the e-CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the e-CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the e-CRF entries against the source documents, except for the pre-identified source data directly recorded in the e-CRF. The informed consent form will include a statement by which the patient allows the Sponsor’s duly authorized

personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the e-CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF ELECTRONIC CASE REPORT FORMS (E-CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate e-CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All e-CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the e-CRFs, the Investigator’s Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff/Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio;
- Patient enrollment is unsatisfactory;
- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;
- Non-compliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP;
- The total number of patients are included earlier than expected;

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

16 BIBLIOGRAPHIC REFERENCES

1. Zhang L, Wang F, Wang L, Wang W, Liu B, Liu J, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. Lancet. 2012 Mar 3;379(9818):815-22.

2. Imai E, Horio M, Watanabe T, Iseki K, Yamagata K, Hara S, et al. Prevalence of chronic kidney disease in the Japanese general population. Clin Exp Nephrol. 2009 Dec;13(6):621-30.

3. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007 Nov 7;298(17):2038-47.

4. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009 Aug;(113):S1-130.

5. Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. JAMA. 2011 Mar 16;305(11):1119-27.

6. Chen N, Wu X, Ding X, Mei C, Fu P, Jiang G, et al. Sevelamer carbonate lowers serum phosphorus effectively in haemodialysis patients: a randomized, double-blind, placebocontrolled, dose-titration study. Nephrol Dial Transplant. 2014 Jan;29(1):152-60.

7. Ketteler M, Rix M, Fan S, Pritchard N, Oestergaard O, Chasan-Taber S, et al. Efficacy and tolerability of sevelamer carbonate in hyperphosphatemic patients who have chronic kidney disease and are not on dialysis. Clin J Am Soc Nephrol. 2008 Jul;3(4):1125-30.

8. Perry CM, Plosker GL. Sevelamer carbonate: a review in hyperphosphataemia in adults with chronic kidney disease. Drugs. 2014 May;74(7):771-92.

9. Renvela EARP Summary for the public (2009 June). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000993/WC500052613.pdf. Retrieved June 2014.

10. US FDA Renvela Label Information (2011 June). Available at:http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo. Retrieved June 2014.

11. Guidance for Diagnosis and Treatment of Mineral and Bone Disorder in Chronic Kidney Disease (2013 December). Available at:http://www.csnchina.org/uploadfiles/img/file/20131202/20131202150017091709.pdf. Retrieved June 2014.

12. Bleyer AJ, Burke SK, Dillon M, Garrett B, Kant KS, Lynch D, et al. A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. Am J Kidney Dis. 1999 Apr;33(4):694-701.

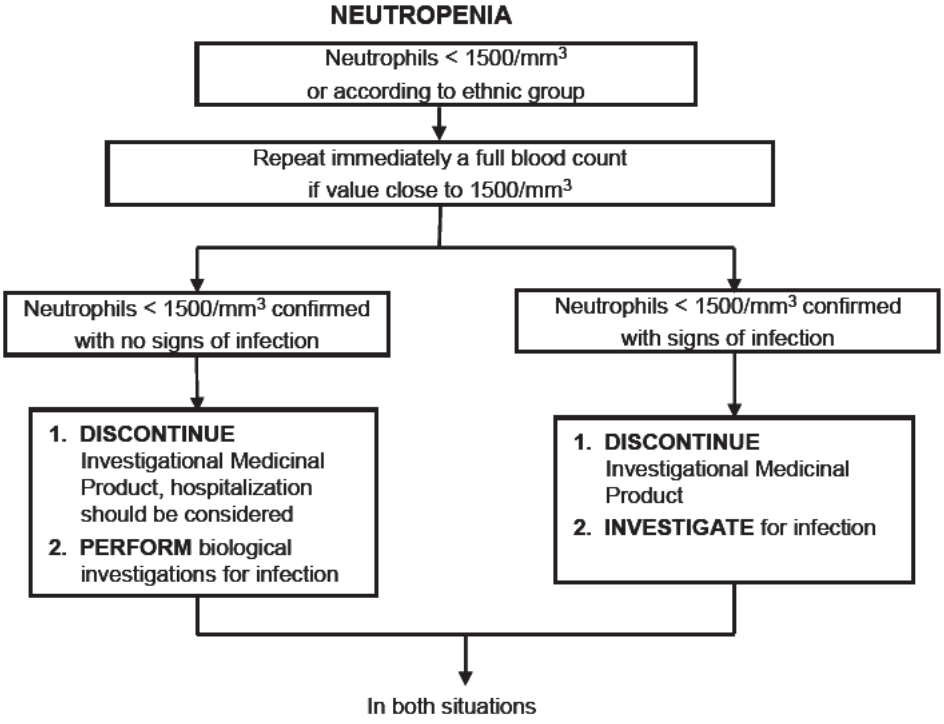
13. Slatopolsky EA, Burke SK, Dillon MA. RenaGel, a nonabsorbed calcium- and aluminum-free phosphate binder, lowers serum phosphorus and parathyroid hormone. The RenaGel Study Group. Kidney Int. 1999 Jan;55(1):299-307.

14. Wilkes BM, Reiner D, Kern M, Burke S. Simultaneous lowering of serum phosphate and LDL-cholesterol by sevelamer hydrochloride (RenaGel) in dialysis patients. Clin Nephrol. 1998 Dec;50(6):381-6.

15. Braun J, Asmus HG, Holzer H, Brunkhorst R, Krause R, Schulz W, et al. Long-term comparison of a calcium-free phosphate binder and calcium carbonate--phosphorus metabolism and cardiovascular calcification. Clin Nephrol. 2004 Aug;62(2):104-15.

17 APPENDICES

Appendix A Guidance for the follow-up of laboratory abnormalities by Sanofi



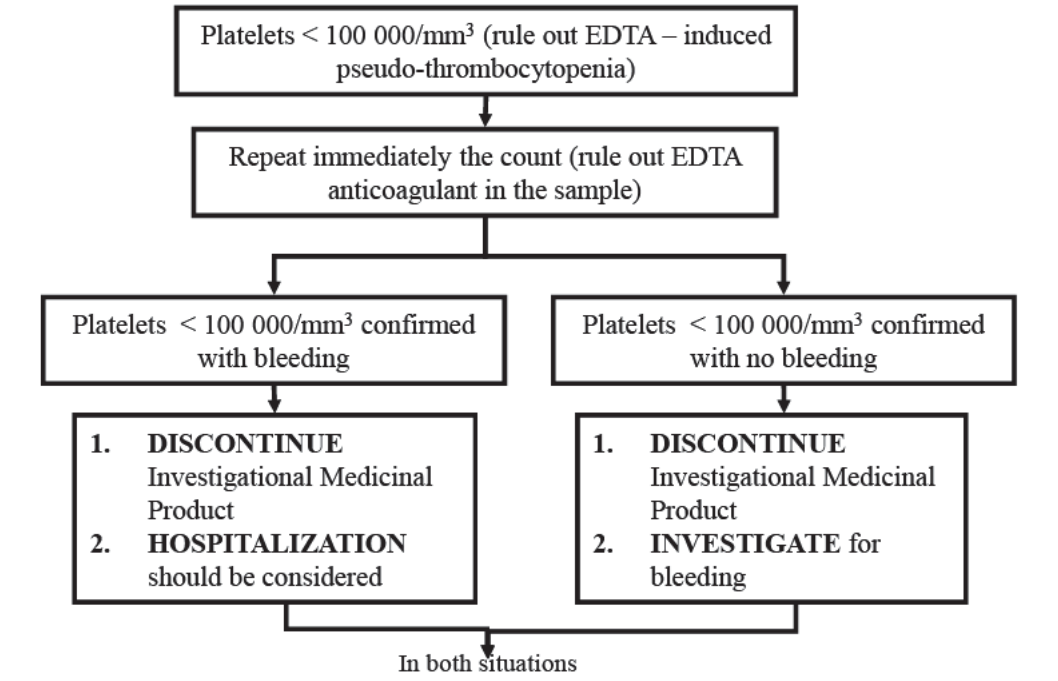
Note

- The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations) , an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
- For individuals of African descent, the relevant value of concern is <1000/mm3

Neutropenia are to be recorded as AE only if they are :

- Symptomatic, and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion [in that case, the event (SAE) should be notified within ***24 hours*** to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI) with immediate notification

THROMBOCYTOPENIA

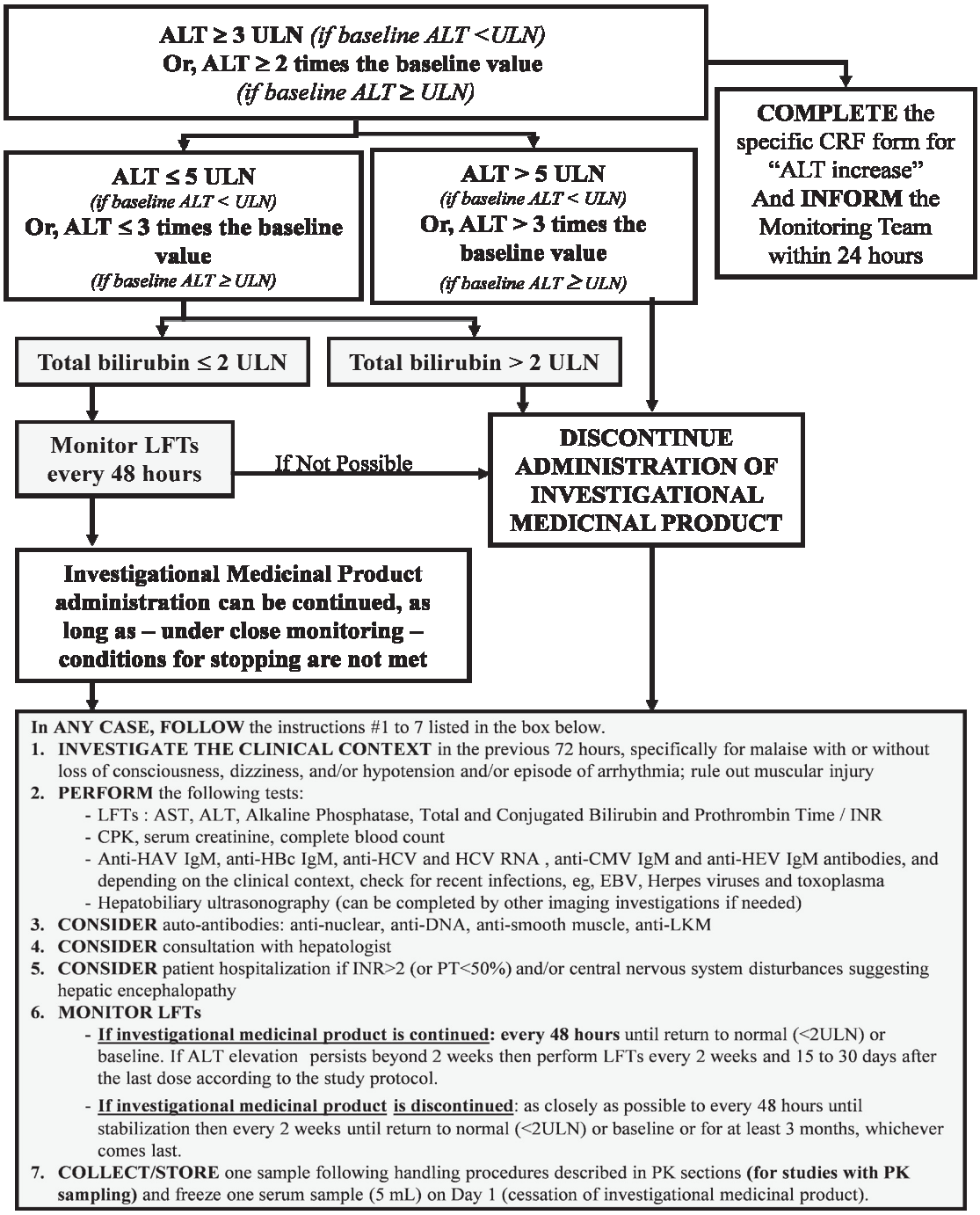


3. **INFORM** the local Monitor
4. **QUESTION** about last intake of quinine (drinks), alcoholism, heparin administration
5. **PERFORM** or collect the following investigations:
   - Complete blood count, schizocytes, creatinine
   - Bleeding time and coagulation test (fibrinogen, INR or PT, aPTT), Fibrin Degradation Product
   - Viral serology: EBV, HIV, mumps, measles, rubella
6. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
7. **DECISION** for bone marrow aspiration: to be taken in specialized unit
   - On Day 1 in the case of associated anemia and/or leukopenia
   - On Day 8 if platelets remain < 50 000/mm³
8. **MONITOR** the platelet count every day for at least one week and then regularly until it returns to normal

Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

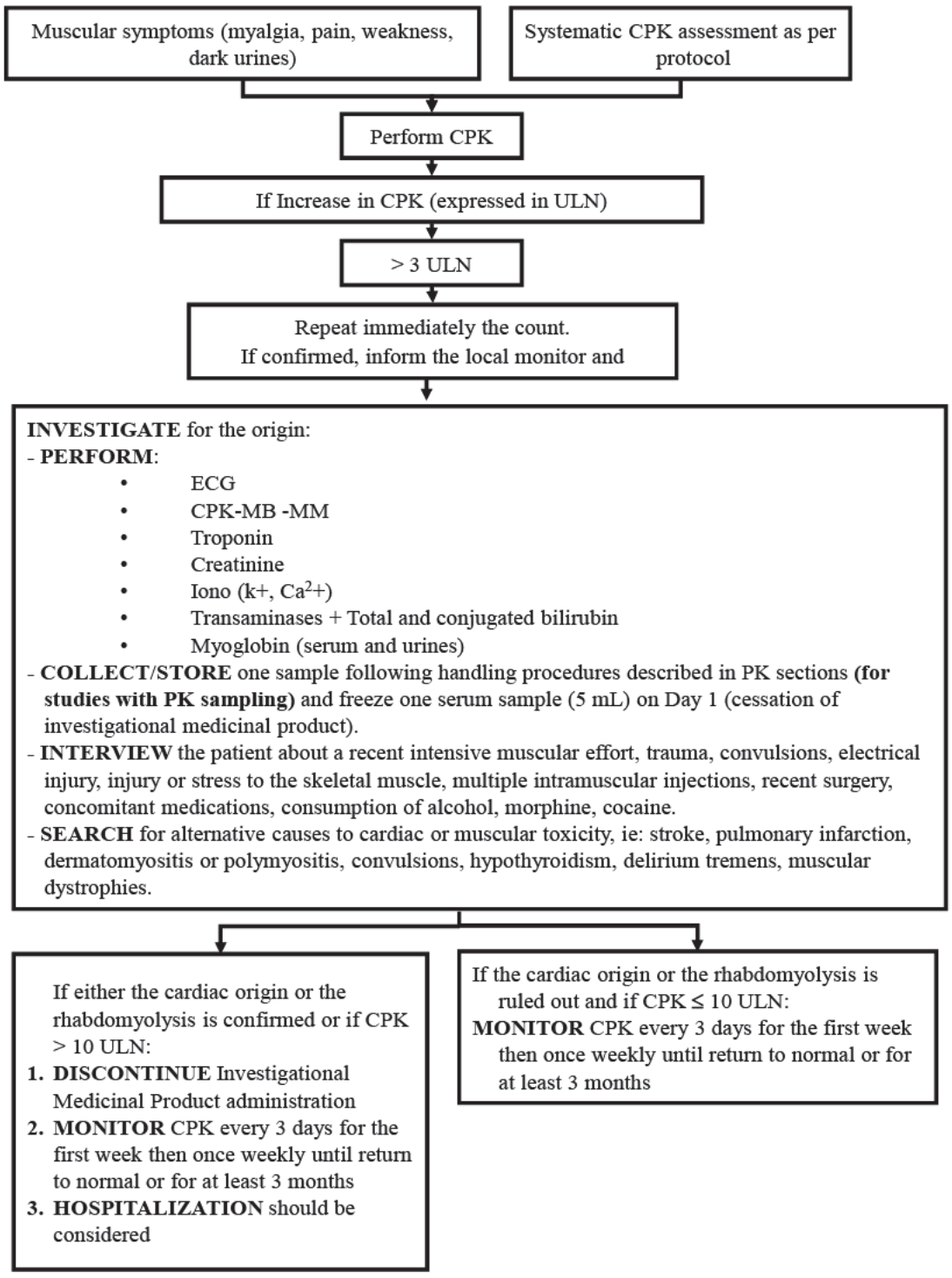
Thrombocytopenia is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met

INCREASE IN ALT



NOTE: ALT ≥3 ULN (IF BASELINE ALT < ULN) OR ALT ≥2 TIMES THE BASELINE VALUE (IF BASELINE ALT ≥ ULN) SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM (SEE SECTIONS 10.4.1.3 AND 10.4.5). IN ADDITION, IF ALT <3 ULN MEETS A SERIOUSNESS CRITERION, THE EVENT SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM

SUSPICION OF RHABDOMYOLYSIS



Suspicion of rhabdomyolysis is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met

EFC14011 Amended Protocol02

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	[redacted]
	Regulatory Approval	
	Clinical Approval	